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Improved Synthesis of the C-Glucuronide/Glycoside of 4-Hydroxybenzylretinone (4-HBR)

Kathryn R. Cavanaugh¹, Sureshbabu Narayanasamy^{1,2}, Joel R. Walker¹, Margaret Clagett-Dame^{3,4}, and Robert W. Curley Jr¹

¹Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, Ohio, USA

²Department of Human Nutrition, The Ohio State University, Columbus, Ohio, USA

³Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin-Madison, Madison, Wisconsin, USA

⁴Pharmaceutical Sciences Division, School of Pharmacy, University of Wisconsin-Madison, Madison, Wisconsin, USA

Abstract

Improvements in the synthesis of carbon-linked glucuronide/glucoside conjugates of cancer chemopreventive retinoids have been achieved starting with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose. The revised approach demonstrates better yields, eliminates the use of an expensive, carcinogenic protecting group reagent, and avoids much painstaking chromatography. The new approach should allow synthesis of larger quantities of the agents for detailed animal and mechanistic studies.

Keywords

C-Glucuronide; C-Glycoside; Retinoid; Synthesis; Chemopreventives

INTRODUCTION

Drugs and xenobiotics are frequently metabolized by conjugation with glucuronic acid. These conjugates typically have good water solubility and are relatively readily eliminated in urine or bile. The vitamin A metabolite retinoic acid (RA; **1**) is known to form an *O*-acyl glucuronide metabolite.^[1] RA and its analogs (retinoids) have long been of interest as potential cancer chemopreventives or chemotherapeutics because of the essential role for RA in the differentiation of epithelial tissues.^[2] It is rarely found that the glucuronide conjugates of drugs and hormones retain the biological activity of the parent molecule.^[3] In the case of retinoyl β -glucuronide (**2**), it has been suggested that this might be an active antiproliferative metabolite of RA.^[4] The semisynthetic retinoid *N*-(4-hydroxyphenyl)retinamide (4-HPR; **3**) has generated interest as a less toxic analog of **1** showing good activity in cancer

chemoprevention and therapy.^[5] Some evidence suggested that **3** might also form a glucuronide conjugate (**4**) and that this might be an active mammary tumor chemopreventive agent.^[6] We prepared **4** and confirmed it is more potent and less toxic than **3** as a mammary tumor chemopreventive/therapeutic.^[7–9] Since **4** is a substrate for β -glucuronidase and other hydrolytic processes, we prepared a number of unhydrolyzable, carbon-linked analogs^[10,11] of this oxygen-linked **4** and found that, in particular, the 4-HPR-*C*-glucuronide (**5**) showed even better activity in a carcinogen-induced rat mammary tumor model.^[12] This strongly suggested that these glucuronide metabolites were active as intact conjugates.

While 4-HPR is less toxic than **1**, it is still possible for **3** to be hydrolyzed *in vivo* to generate RA. Our evidence suggests that this hydrolysis does occur to some extent and might account for the remaining toxicity, including some residual teratogenicity of **3**.^[13] Therefore, we have also prepared the unhydrolyzable ketone analog of **3**, 4-hydroxybenzylretinone (4-HBR; **6**).^[14] This ketone retains the tumor inhibitory properties of **3** but had the hoped for reduction in toxicity, presumably since no hydrolysis to RA can occur.^[15] A compound combining these two structural themes (an unhydrolyzable *C*-glucuronide and a ketone substitution for an amide) could result in the most effective, least toxic analog in this series. Therefore, we prepared 4-HBR-*C*-glucuronide (4-HBRCG; **7**).^[16] This synthesis allowed us to prepare a modest amount of **7** and preliminary experiments showed it to be relatively non-toxic and effective in mammary tumor chemotherapy.^[16] We also prepared a small amount of the *C*-glucoside analog **8** as a model compound. To our surprise, this analog showed some interesting preliminary growth inhibitory activity *in vitro*^[17] and thus a more robust synthesis of both **7** and **8** is needed to facilitate further studies. We report here recent improvements in the preparation of these carbon-linked analogs which feature modifications in the carbohydrate components of the syntheses.

RESULTS AND DISCUSSION

The original synthesis of **7** is published^[16] and only important elements are shown in Scheme 1 to aid discussion. Key intermediate **10** was made by subjecting olefin **9** to the hydroboration/Suzuki-Miyaura cross coupling sequence developed by Johnson and co-workers for the synthesis of C-disaccharides.^[18] While the sequence generally provided intermediates in good yields, a number of issues made it not amenable for scale-up synthesis. These included the expense and toxicity of the chloromethyl methyl ether needed to prepare precursors to **9**. In addition, nearly all of the intermediates in the synthetic scheme were oils which required careful chromatography, even for those substances that eventually crystallized (*e.g.* **11** and **12**).

Since the Petasis^[19] and hydroboration/Suzuki sequence had previously been successfully employed with benzyl-protected sugars,^[20] we turned to the commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**13**) as starting material for the revised synthesis of **7** and **8**. Swern-type oxidation (DMSO, Ac₂O) of **13** provides lactone **14** as the only oil in the revised synthesis, which was purified after rapid “column filtration” through silica gel (Scheme 2). Subsequent products **15** and **16** were also purified in the same way unless they are prepared on smaller scale (<20 g), in which case both of these solids can be purified by recrystallization without the need for removal of side products which on the larger scale

hinder direct crystallization. Lactone **14** is converted to olefin **15** using Petasis reagent much more smoothly than using Tebbe's reagent.^[21] We do find that it is preferable to prepare the Petasis reagent freshly for each use. This white, solid enol ether **15** is stable for up to one month at room temperature. Hydroboration/Suzuki cross coupling of **15** with 4-bromotoluene provided the *C*-glucoside **16**. However, unlike for the preparation of **10** from **9** (Scheme 1) in this case, when we used 4-iodotoluene instead of the bromide, **16** was obtained in the expected higher yield. Previously, we and others have shown that hydroboration with 9-BBN followed by the Pd-coupling provides the β -stereochemistry at the former anomeric carbon center of the sugar.^[16, 20, 21, 22] All of the NMR data obtained for **16** supports the conclusion that the same is true for this coupling reaction. Catalytic hydrogenolysis of **16** provided the tetrol analog of **16** which was used as obtained. Conditions were developed which permitted this process to be carried out at room temperature, with atmospheric pressure of hydrogen,^[23] and without the use of acid catalysis which resulted in a cleaner product.

Selective, TEMPO-mediated oxidation of the 6-hydroxymethyl group of the tetrol derived from **16**, followed by reprotection provided the *C*-glucuronide **17** in a manner analogous to the previous approach (see Scheme 1).^[16] Bromination of **17** gave primary bromide **12** almost exclusively. Trace additional bromides/dibromides that form can be substantially removed by crystallization. Analytically pure samples are isolated by preparative HPLC however any trace impurities remaining after crystallization, mainly dibromide, do not interfere with alkylation of *umpolung*-activated retinal (**18**; figure 1) and isolation of that product. Alternatively, acetylation of the tetrol provided *C*-glucoside **19** which was brominated to give **20** as for the formation of **12**. Interestingly, these brominations seem to proceed more completely and with fewer minor side products as the scale of the reaction is increased.

In summary, this paper describes more efficient syntheses of key *C*-glycoside intermediates **12** and **20**. It avoids the need for the highly toxic chloromethyl methyl ether, most of the intermediates are crystallizable solids, bypasses much of the tedious chromatography, and the cost is roughly one third and two thirds of the previous method for the synthesis of the *C*-glucoside and *C*-glucuronide respectively. Alkylation of these bromides with the *umpolung*-activated aldehyde **18** as we have previously done,^[16] requires the relatively expensive polyene retinal (**18**). Our recent improvements in the preparation of **18**^[24, 25] have further contributed to a substantial decrease in the cost of the syntheses of these *C*-glucuronides/glycosides. This should make larger scale study of the antitumor properties and mechanism(s) of action of **7** and **8** feasible.

EXPERIMENTAL

General Methods

¹H and ¹³C NMR spectra were recorded on a Bruker DRX400 instrument at 400 and 100 MHz respectively. Melting points were measured on a Thomas-Hoover capillary apparatus. Optical rotations were recorded on a Perkin-Elmer 343 polarimeter. Infrared spectra were collected on a Thermo-Nicolet 6700 FTIR. High resolution electrospray ionization/time of

flight mass spectra were recorded at the OSU Campus Chemical Instrument Center on a Bruker maXis 4G instrument. TLC was performed on silica gel 60 F₂₅₄ precoated aluminum-backed plates and column “filtration”/chromatography was performed on silica gel 60, 70–230 mesh. Analysis and separation by HPLC was conducted on a Beckman unit (model 127 pump, model 166 detector) using a Zorbax-Sil 4.6 × 250 mm column (4:1 hexane/ethyl acetate at 2 mL/min.) or Zorbax-Sil 9.4 × 250 mm column (3:1 hexane/ethyl acetate at 5 mL/min.) respectively, with monitoring at 265 nm. The 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose was purchased from Alfa Aesar. The [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), referred to as PdCl₂(dppf), was obtained from Frontier Scientific.

2,3,4,6-Tetra-*O*-benzyl-D-gluconic acid-6-lactone (**14**)^[26,27]

To an oven-dried flask under Ar was added 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**13**; 1.88 g; 3.49 mmol) and dissolved in 11 mL dry DMSO. Dry acetic anhydride (7.3 mL) was added and the mixture stirred at rt overnight. The solution was poured into ice water and extracted with ether (3 × 50 mL). The combined organic layer was washed successively with saturated NaHCO₃ and NaCl (brine) solutions, dried (Na₂SO₄), filtered and solvent removed under reduced pressure. Product was purified via rapid filtration through silica gel using 15% ethyl acetate/hexanes. The resulting oil was sparged with compressed air overnight to give clear oil **14** which was used as obtained (1.25 g; 67% yield): [α]_D²⁰ +69.5 (*c* 0.14, CHCl₃); ¹H NMR (CDCl₃) δ 7.44–7.15 (m, 20H), 5.01 (d, 1H, *J* = 11.4 Hz), 4.76–4.45 (m, 7H), 4.45 (dd, 1H, *J* = 2.0, 13.9 Hz), 3.93 (dd, 2H, *J* = 6.5, 10.6 Hz), 3.72 (dd, 2H, *J* = 2.2, 3.2 Hz); ¹³C NMR ((CD₃)₂CO) δ 170.17, 139.20, 139.10, 139.02, 138.67, 129.22, 129.19, 129.18, 129.04, 128.88, 128.72, 128.64, 128.58, 128.47, 81.73, 78.94, 78.56, 76.81, 73.99, 73.82, 73.81, 73.76, 68.99; IR (cm⁻¹) 3027, 2872, 1951, 1878, 1758.

Petasis reagent (dimethyltitanocene)^[17]

To an oven-dried, Al foil wrapped flask under Ar was added titanocene dichloride (2.5 g, 10 mmol) and absolute ether (50 mL) and cooled to 10°C. Methyl lithium (1.6M in ether; 15 mL) was added dropwise. The cooling bath was then removed and the solution was stirred at rt for 10 min. The reaction mixture was cooled in an ice bath and ice cold water added. In the dark, the aqueous layer was extracted 3 × 50 mL with ether. The combined organic layer was dried (Na₂SO₄) and sparged with Ar for 1hr. The product was filtered and concentrated in the dark at rt to give an orange solid which was diluted with toluene (20 mL; 0.5 M) and used without further purification.

2,6-Anhydro-1-deoxy-3,4,5,7-tetra-*O*-benzyl-D-gluc-hept-1-enitol (**15**)^[28,29]

To an oven-dried 3-neck flask under Ar was added lactone **14** (1.08 g; 2 mmol) in 10 mL toluene. The flask was wrapped in Al foil and 10 mL of 0.5 M Petasis reagent solution in toluene added dropwise (or at once on larger scale) via an Al foil wrapped syringe. The mixture was heated to 70°C in an oil bath and stirred for 3–5 days in the dark with monitoring by TLC (20% ethyl acetate/hexanes). The reaction mixture was poured into 2–2.5 volumes of hexanes and vacuum filtered through diatomaceous earth. The diatomaceous earth was washed with additional hexanes and solvent removed under reduced pressure to

give a bright yellow-orange oil that solidifies upon standing. Crude product was purified by recrystallization (unless the scale is larger than 20 g in which case filtering the yellow-orange solid loaded on silica gel through silica gel with hexanes then 5% ethyl acetate/hexanes solution gives a yellow oil that solidifies upon standing). Product was then recrystallized from hexanes to give **15** as white needle crystals (0.75 g, 70% yield): m.p. 67–67.5 °C (lit. m.p. 60–62 °C); $[\alpha]_D^{20} +52$ (c 0.24, CHCl_3); ^1H NMR ($(\text{CD}_3)_2\text{CO}$) δ 7.31–7.22 (m, 20H), 4.79–4.46 (m, 10H), 3.99 (d, 1H, $J = 4.5$ Hz), 3.84 (m, 1H), 3.75–3.67 (m, 4H); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) δ 157.23, 139.27, 138.98, 138.93, 138.77, 129.24, 129.16, 129.09, 128.77, 128.76, 128.73, 128.58, 128.50, 128.40, 128.37, 128.32, 93.92, 84.86, 79.22, 78.65, 78.46, 74.44, 73.99, 73.86, 72.39, 69.89; HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{35}\text{H}_{36}\text{O}_5\text{Na}$ 559.2461; Found 559.2474; IR (cm^{-1}) 3065, 2986, 2306.

2,6-Anhydro-1-deoxy-1-[4-(methyl)phenyl]-3,4,5,7-tetra-O-benzyl-D-glycero-D-gulo-heptitol (**16**)^[18]

To a flame dried flask under Ar was add enitol **15** (1.5 g; 2.8 mmol) in dry THF (28 mL). A 0.5M solution of 9-BBN in THF (2.5 mmol; 14 mL) was added dropwise and the mixture refluxed for 4.5 hours. After cooling to rt and adding 2.2 mL 3M K_3PO_4 (2.4 eq) and stirring for 10 minutes, 4-iodotoluene (0.7 g; 3 mmol) and $\text{PdCl}_2(\text{dppf})$ (0.2 g, 0.22 mmol) dissolved in dry DMF (28 mL) were added dropwise and the mixture stirred for 18 h. The mixture was diluted with ethyl acetate and the layers separated. The aqueous layer was extracted 3 $\times$ 75 mL with ethyl acetate. The combined organic layers were washed with water, brine and dried (MgSO_4), filtered, and concentrated to a brown solid which was recrystallized (unless the scale is greater than 20 g in which case the solid was rapidly filtered through silica gel with 10% ethyl acetate/hexanes to give white/yellow crystals). Recrystallization from hexanes gave a white solid **16** (2.1 g, 77% yield); m.p. 88.5–90 °C; $[\alpha]_D^{20} +25.6$ (c 0.20, CHCl_3); ^1H NMR ($(\text{CD}_3)_2\text{CO}$) δ 7.35–7.25 (m, 20H), 7.15 (d, 4H, $J = 7.9$ Hz), 7.01 (d, 2H, $J = 7.8$ Hz), 4.95–4.86 (m, 3H), 4.81 (d, 1H, $J = 11.0$ Hz), 4.71 (d, 1H, $J = 11.2$ Hz), 4.64 (d, 1H, $J = 11.0$ Hz), 4.52 (dd, 2H, $J = 9.2, 12.2$ Hz), 3.69 (m, 3H), 3.56 (dd, 1H, $J = 9.6, 19.8$ Hz), 3.48 (ddd, 1H, $J = 2.2, 6.8, 9.1$ Hz), 3.38 (dd, 1H, $J = 2, 6.4$ Hz), 3.29 (dd, 1H, $J = 9.0, 18.3$ Hz), 3.10 (dd, 1H, $J = 1.8, 14.3$ Hz), 2.81 (d, 1H, $J = 5.4$ Hz), 2.65 (dd, 1H, $J = 5.4, 8.9$ Hz), 2.24 (s, 3H); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) δ 140.07, 139.95, 139.85, 139.72, 136.93, 136.06, 130.36, 129.55, 129.16, 129.13, 129.10, 129.05, 128.67, 128.65, 128.38, 128.34, 128.23, 128.13, 88.12, 82.82, 80.76, 79.95, 79.71, 75.87, 75.44, 75.33, 73.82, 70.22, 38.31, 21.12; HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{42}\text{H}_{44}\text{O}_5\text{Na}$ 651.3087; Found 651.3112; IR (cm^{-1}) 3018, 2917, 2404, 1954, 1881, 1815.

2,6-Anhydro-1-deoxy-1-[4-(methyl)phenyl]-D-glycero-D-gulo-heptitol^[30]

To an oven dried flask under Ar was add 1 g 10% Pd/C and the flask flushed with argon and evacuated to remove O_2 . Benzyl protected **16** (6.68 g; 10.6 mmol) was added in 53 mL dichloromethane under Ar and after using vacuum and Ar to fully evacuate air, 53 mL of CH_3OH was added slowly with stirring at rt. Vacuum and a H_2 balloon was used alternately to charge the system with hydrogen, and stirring continued overnight or until the reaction was complete. When reaction was complete (determined to be when R_f goes to zero by TLC in 20% ethyl acetate/hexanes) the Pd/C was filtered off through diatomaceous earth and

washed with CH₃OH/H₂O and the filtrate concentrated. The debenzylated product tetrol was used without further purification.

2,6-Anhydro-7-deoxy-7-[4-(methyl)phenyl]-3,4,5-tri-O-acetyl-L-glycero-L-gulo-heptinoic acid methyl ester (17)

To a round bottomed flask was added TEMPO (1.0 g; 6.4 mmol), KBr (0.75 g, 6.4 mmol) and 125 mL of saturated NaHCO₃ and the mixture stirred at 0 °C for 20 min. Commercial grade bleach (3.5 mL) was added and the mixture stirred at 0 °C for 10 min. The debenzylated tetrol derived from **16** above (0.38 g; 1.42 mmol) was dissolved in 7.5 mL CH₃CN and along with 25 mL of saturated NaHCO₃ was added to the TEMPO solution and stirred for 45 min. at 0 °C. At 25 min. a pH drop of the reaction mixture was noted and an additional 7.5 mL of saturated NaHCO₃ added. Ethanol (15 mL) was added and the mixture was washed with ether. The aqueous layer was then concentrated to dryness and the resulting solid was stirred with CH₃OH overnight and the residue filtered and the alcohol concentrated. To the residue was added 50 mL DMF and then iodomethane (1.2 mL; 19.3 mmol) was added and stirring continued at rt under Ar for 24 hrs. Acetic anhydride (15 mL; 159 mmol) was added to the solution along with pyridine (7.5 mL; 92.9 mmol) and 5 mg of DMAP and the mixture was stirred for 48 hr at rt. Liquids were evaporated under a stream of air over 3 days and the residue partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried (MgSO₄), filtered, concentrated under reduced pressure, and chromatographed (2:1 then 1:1 hexanes/ethyl acetate) to give an off-white solid which was recrystallized from hexanes to give white solid **17** (0.514 g, 86% yield): m.p. 100–102 °C; [α]_D²⁰ –0.051 (*c* 0.07, CHCl₃); ¹H NMR ((CD₃)₂CO) δ 7.09 (d, 2H, *J* = 8.0 Hz), 7.06 (d, 2H, *J* = 7.9 Hz), 5.29 (dd, 1H, *J* = 9.3, 10.1 Hz), 5.05 (dd, 1H, *J* = 9.7, 10.3 Hz), 4.89 (dd, 1H, *J* = 9.6, 10.1 Hz), 4.15 (d, 1H, *J* = 10.0 Hz), 3.90 (m, 1H), 3.62 (s, 3H), 2.86 (dd, 1H, *J* = 3.2, 14.6 Hz), 2.72 (dd, 1H, *J* = 8.1, 14.5 Hz), 2.24 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.94 (s, 3H); ¹³C NMR ((CD₃)₂CO) δ 170.40, 170.16, 169.99, 168.50, 136.56, 135.21, 130.27, 129.66, 78.77, 76.44, 74.14, 72.57, 70.67, 52.77, 38.03, 21.07, 20.69, 20.62, 20.49; HRMS (ESI-TOF) *m/z*: [M+Na]⁺ Calcd for C₂₁H₂₆O₉Na 445.1475; Found 445.1511 ; IR (cm⁻¹) 3062, 2803, 1672.

2,6-Anhydro-7-deoxy-7-[4-(bromomethyl)phenyl]-3,4,5-tri-O-acetyl-L-glycero-L-gulo-heptinoic acid methyl ester (12)^[16]

To an oven dried flask under Ar was added 127 mg (0.3 mmol) of **17** and dissolved in 2.5 mL of dry CCl₄. Recrystallized NBS (51 mg; 0.36 mmol) and benzoyl peroxide (2.3 mg; 0.012 mmol) were added and the mixture refluxed for 2 hr. After cooling to rt the mixture was filtered and the filtrate concentrated under reduced pressure. The resulting crude solid was chromatographed (3:2 hexanes/ethyl acetate) and further purified by recrystallization from 20% ethyl acetate in hexanes to give a white solid **12** (88 mg, 74% yield) identical to our previously prepared **12**.^[16] Selected analytical data: HPLC *t*_R = 13.8 min. (4:1 hexane/ethyl acetate); ¹H NMR ((CD₃)₂CO) δ 7.39 (d, 2H, *J* = 8.1 Hz), 7.27 (d, 2H, *J* = 8.1 Hz), 5.32 (dd, 1H, *J* = 9.4, 11.3 Hz), 5.07 (dd, 1H, *J* = 9.4, 11.8 Hz), 4.93 (dd, 1H, *J* = 9.8, 10.4 Hz), 4.65 (s, 2H), 4.22 (d, 1H, *J* = 9.9 Hz), 3.97–4.06 (m, 1H), 3.68 (s, 3H), 2.94 (dd, 1H, *J* = 3.5, 14.6 Hz), 2.78–2.87 (m, 1H), 1.98 (s, 3H), 1.963 (s, 3H), 1.959 (s, 3H); ¹³C NMR ((CD₃)₂CO) δ 170.39, 170.18, 170.01, 168.49, 138.78, 137.35, 130.79, 129.99, 78.52, 76.40,

74.12, 72.63, 70.66, 52.82, 38.20, 34.50, 20.72, 20.62, 20.51; HRMS (ESI) m/z : $[M+H]^+$
Calcd for $C_{21}H_{26}BrO_9$ 507.07547; Found 507.07542.

2,6-Anhydro-1-deoxy-1-[4-(methyl)phenyl]-3,4,5,7-tetra-O-acetyl-D-glycero-D-gulo-heptitol(19)

The debenzylated tetrol derived from **16** above (2.84 g; 10.6 mmol) was dissolved in 383 mL DMF. After addition of 32 mg DMAP, 85 mL acetic anhydride (899 mmol), and 43 mL pyridine (532 mmol), the mixture was stirred for 18 hr under Ar at rt. After addition of cold water the mixture was extracted with ethyl acetate (3×75 mL) and the combined organic layer was washed with water, brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give crude solid which was recrystallized twice from hexanes to give white solid **19** (3.74 g, 81% yield): m.p. 122–124°C; $[\alpha]_D^{20} -5.2$ (c 0.06, $CHCl_3$); ^1H NMR ($(CD_3)_2CO$) δ 7.10 (d, 2H, $J = 8.0$ Hz), 7.05 (d, 2H, $J = 7.9$ Hz), 5.22 (dd, 1H, $J = 9.4$, 9.9 Hz), 4.97 (dd, 1H, $J = 9.8$, 10.1 Hz), 4.85 (dd, 1H, $J = 9.5$, 9.8 Hz), 4.22 (dd, 1H, $J = 5.9$, 12.3 Hz), 4.00 (dd, 1H, $J = 2.4$, 12.2 Hz), 3.74–3.84 (m, 2H), 2.81 (m, 1H), 2.67 (dd, 1H, $J = 8.5$, 14.3 Hz), 2.25 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.93 (s, 3H); ^{13}C NMR ($(CD_3)_2CO$) δ 170.65, 170.44, 170.21, 170.12, 136.43, 135.53, 130.30, 129.54, 78.76, 76.40, 76.07, 74.92, 72.83, 69.75, 63.04, 37.98, 21.03, 20.69, 20.68, 20.63, 20.60; HRMS (ESI-TOF) m/z : $[M+Na]^+$ Calcd for $C_{22}H_{28}O_9Na$ 459.1632; Found 459.1661; IR (cm^{-1}) 2925, 2853, 1660.

2,6-Anhydro-1-deoxy-1-[4-(bromomethyl)phenyl]-3,4,5,7-tetra-O-acetyl-D-glycero-D-gulo-heptitol(20)^[17]

To oven dried glassware under Ar was added acetate **19** (3.2 g; 7.3 mmol) and dissolved in 73 mL CCl_4 . NBS (1.6 g; 8.8 mmol) and benzoyl peroxide (0.07 g; 0.3 mmol) were added and the mixture refluxed for 2 hr. After cooling to rt the mixture was filtered and the filtrate concentrated under reduced pressure to give crude solid which was chromatographed (3:2 hexanes/ethyl acetate) and recrystallized from 40% ethyl acetate in hexanes to give white solid **20** (2.7 g, 71% yield): m.p. 133–135 °C; $[\alpha]_D^{20} -15.0$ (c 0.22, $CHCl_3$); HPLC $t_R = 14.4$ min. (4:1 hexane/ethyl acetate); ^1H NMR ($(CD_3)_2CO$) δ 7.35 (d, 2H, $J = 8.1$ Hz), 7.22 (d, 2H, $J = 8.1$ Hz), 5.2 (dd, 1H, $J = 9.4$, 18.9 Hz), 4.94 (dd, 1H, $J = 9.8$, 19.5 Hz), 4.84 (dd, 1H, $J = 9.6$, 19.2 Hz), 4.60 (s, 2H), 4.2 (dd, 1H, $J = 5.9$, 12.2 Hz), 3.96 (dd, 1H, $J = 2.3$, 12.0 Hz), 3.85 (m, 2H), 2.84 (d, 1H, $J = 3.1$ Hz), 2.72 (dd, 1H, $J = 3.0$, 8.6 Hz), 2.00 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.95 (s, 3H); ^{13}C NMR ($(CD_3)_2CO$) δ 170.47, 170.26, 170.05, 169.93, 138.86, 137.06, 130.61, 129.67, 78.32, 75.97, 74.75, 72.73, 69.63, 62.95, 37.99, 34.28, 20.76, 20.72, 20.63, 20.61; HRMS (ESI-TOF) m/z : $[M+Na]^+$ Calcd for $C_{22}H_{27}BrO_9Na$ 537.0736; Found 537.0724; IR (cm^{-1}) 3018, 2952, 2401, 1755.

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1 R = OH

18 R = H

4 X = NH, Y = O, R = COOH

5 X = NH, Y = CH₂, R = COOH

7 X = CH₂, Y = CH₂, R = COOH

8 X = CH₂, Y = CH₂, R = CH₂OH

Figure 1.
Structures of Retinoids.

Scheme 1.

Reagents and conditions: (a) (i) 9-BBN-H, THF, reflux, 6 h; (ii) $\text{PdCl}_2(\text{dppf})$, 3M K_3PO_4 , DMF, 4-bromobenzyl alcohol, 18 h, 67%; (b) (i) NaH, THF, 1.5 h; (ii) CH_3I , 18 h, 90%; (c) (i) 6 N HCl, MeOH, 18 h; (ii) TEMPO, NaClO, KBr, NaHCO_3 , 0 °C, 45 min; (iii) CH_3I , DMF, 20 h; (iv) Ac_2O , pyridine, DMAP, 18 h, 82%; (d) HBr, AcOH, 18 h, 86%.

Scheme 2.

Reagents and conditions: (a) Ac_2O , DMSO, 18 h, 67%; (b) $\text{Cp}_2\text{Ti}(\text{CH}_3)_2$, PhCH_3 , 70 °C, 72 h, 70%; (c) (i) 9-BBN-H, THF, reflux, 4.5 h; (ii) $\text{PdCl}_2(\text{dppf})$, 3M K_3PO_4 , DMF, 4-iodotoluene, 18 h, 77%; (d) (i) H_2 , 10% Pd/C; (ii) TEMPO, NaClO, KBr, NaHCO_3 , 0 °C, 45 min; (iii) CH_3I , DMF, 24 h; (iv) Ac_2O , pyridine, DMAP, 48 h, 86%; (e) NBS, benzoyl peroxide, CCl_4 , reflux, 2 h, 74%; (f) (i) H_2 , 10% Pd/C; (ii) Ac_2O , pyridine, DMAP, 18 h, 81%; (g) NBS, benzoyl peroxide, CCl_4 , reflux, 2 h, 71%.